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Bilateral Microphthalmia, Esophageal Atresia, and Cryptorchidism:
The Anophthalmia-Esophageal-Genital Syndrome

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We report on a male infant with bilateral microphthalmia, esophageal atresia, and cryptorchidism. To our knowledge only 4 cases with a similar combination of congenital abnormalities have been previously reported, and it is likely that this represents a distinct entity. We suggest the name "anophthalmia-esophageal-genital-syndrome." Am. J. Med. Genet. 70:171–173, 1997.

KEY WORDS: microphthalmia; esophageal atresia; cryptorchidism

INTRODUCTION

The association of bilateral anophthalmia, esophageal atresia, and glandular hypospadias was described in a male infant by Rogers [1988]; similar findings were reported by Arroyo et al. [1992] and Sandler et al. [1995]. We report on a further infant with the same association of congenital anomalies, and with additional findings at necropsy of abnormal central nervous system appearances, and agenesis of the gallbladder.

CLINICAL REPORT

A male infant was born by normal delivery at 38 weeks of gestation, with birth weight 2.65 kg (3rd–10th centile), length 48 cm (50th centile), and OFC 34 cm (50th centile). Apgar scores were 6 and 8 at 1 and 10 min, respectively. The parents were nonconsanguineous and the family history was unremarkable. The mother was 32 years old, gravida 2 para 2; her present pregnancy was complicated by polyhydramnios. There was no known exposure to drugs or teratogens, although the 29-year-old father may have had some radiation exposure through his work as a submariner. At birth the following were noted: bilateral microphthalmia (Fig. 1), apparently low-set, posteriorly angulated ears with simple flat pinnae (Fig. 2), right facial palsy, unusual palmar creases with distal crease exiting between index and middle fingers (hockey-stick) (Fig. 3), clenched fists with overlapping fingers, micropenis, and right cryptorchidism.

Esophageal atresia was suspected clinically, and confirmed, together with the presence of tracheo-esophageal fistula. Cardiac, renal and abdominal ultrasound, and skeletal survey findings were normal. A CT scan of the brain showed cavum septi pellucidi, and extensive low attenuation of white matter bilaterally, suggesting leukomalacia. A TORCH screen was nonreactive, and chromosomes of peripheral lymphocytes were normal (46,XY).

The baby's abnormalities, and the likelihood of a poor outcome, were discussed with his parents. He was treated palliatively and died following repeated apneic attacks at age 8 days. Autopsy confirmed the presence of bilateral microphthalmia, and of esophageal atresia with distal tracheo-esophageal fistula. Cardiac anatomy was normal. Intraabdominal organs were normal, but the gallbladder was absent. The urinary tract was normal. The testes were small; the right was intraabdominal, and the left was in the inguinal canal. The brain was macroscopically normal. Histologically there was extensive bilateral periventricular leukomalacia in all cerebral lobes, considered to be acute and of perinatal origin. The pituitary gland was normal. There was olfactory aplasia, along with multiple cerebellar cortical heterotopia. Cerebral, brain stem, and cord myelination were assessed as normal.

The manifestations of this case, and those previously described [Rogers, 1988; Arroyo et al., 1992; Sandler et al., 1995], are summarized in Table I.

DISCUSSION

This represents the fifth case report of a combination of microphthalmia, esophageal atresia, and genital underdevelopment, and supports the contention of Arroyo et al. [1992] that this constitutes a new entity. We suggest the name "anophthalmia-esophageal-genital syndrome."

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Fig. 1. Facial view, showing bilateral microphthalmia.

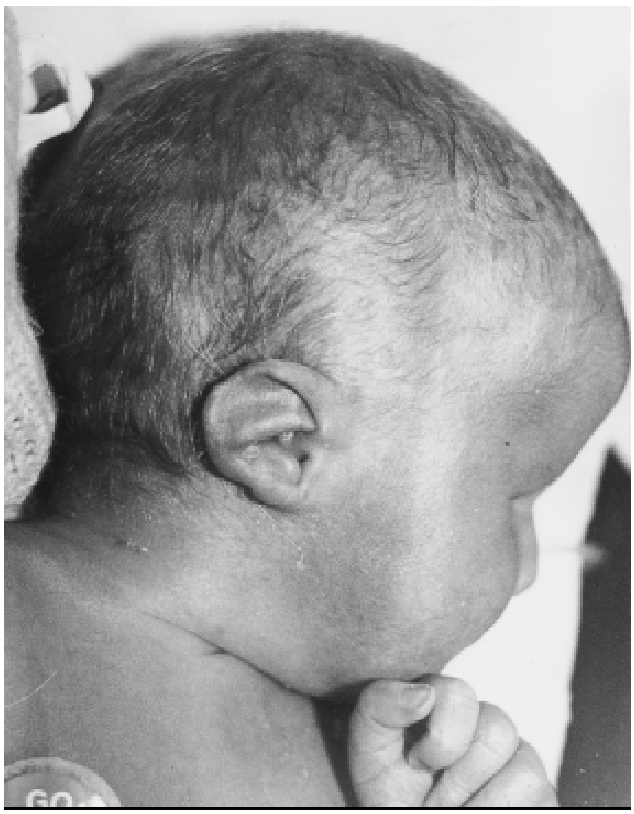

Fig. 2. Lateral view, showing small abnormal right ear.

Fig. 3. "Hockey-stick" palmar crease, right hand.

The finding of olfactory tract hypoplasia in our case, together with hypogonadism, suggests overlap with Kallman syndrome. We consider it likely that the genital hypoplasia is secondary to the central nervous system abnormalities, and to the hypogonadotrophic hypogonadism. Limited support for this is found in the endocrine investigations carried out in case 1 of Sandler et al. [1995]. Phenotypic variability has been observed in Kallmann syndrome [White et al., 1988], including microphthalmia [Jaffe et al., 1987], and a variety of molecular pathologies in the KALIG-1 gene has been described [Franco et al., 1991; Hardelin et al., 1992]. The findings in our case may be compatible with a defect in a neuronal migration factor, with which the KALIG-1 product shares homology [Franco et al., 1991]. However, the demise of our patient means we cannot investigate this further; furthermore, one of the patients of Sandler et al. [1995] was female, making an X-linked condition unlikely.

Autopsy data are not available from previously reported cases, and the significance of the absent gallbladder and of the central nervous system (CNS) pathology in our case is uncertain. Congenital absence of the gallbladder is a rare anomaly, but is described in tracheo-esophageal fistula and anomalies of the genitalia, although not as part of a recognized syndrome [Turkel et al., 1983]. In our case it represents an additional midline embryonic structural defect which could have arisen from a primary developmental field [Opitz and Gilbert, 1982]. The neuropathological appearances were those of cerebral leukomalacia, and histology suggested that this was secondary to ischemia. However, there was no clinical evidence for perinatal hypoxia, and CT changes of extensive white-matter abnormality

TABLE I. Features of Reported Cases

	Rogers [1988]	Arroyo et al. [1992]	Sandler et al. [1995]		Present case
Birth weight (g)	4,000	2,900	3,460	2,600	2,650
Gestation (weeks)	38	38	40	38	38
Sex	M	M	M	F	M
Bilateral anopthalmia/microthalmia	+	+	+	+	+
Esophageal atresia	+	+	+	+	+
Hypospadias/micropenis	+	–	+	–	+
Cryptorchidism	–	+	+	–	+
Abnormal fingers	–	–	–	–	+
Unusual palmar diseases	?	?	–	–	+
"Dysplastic" ears	–	–	–	–	+
CNS abnormality	+	–	+	+	+
Delayed development	+	–	–	+	?
Absent gallbladder	?	?	?	?	+
Karotype	46XY	46XY	46XY	46XX	46XY
Maternal age	?	30	36	26	32
Paternal age	?	32	?	?	29
Consanguinity	?	–	?	?	–

were noted on the third day, antedating the baby's apneic episodes and terminal phase. Although myelination appeared histologically normal, in the 2 cases reported by Sandler et al. [1995], there were MRI brain-scan abnormalities including decreased myelination and brain volume, and ventriculomegaly. It remains possible that the central nervous system abnormalities in our case had the same cause.

This case, in conjunction with the four previous case reports, appears to represent a distinct phenotype. All cases have been sporadic, and the mechanism is unclear at present, although X-linkage is unlikely.

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